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Original Article

Prognostic value of soluble ST2 biomarker in heart failure patients with reduced ejection fraction – A multicenter study

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ABSTRACT

Objective: To study the prognostic value of soluble Suppression of Tumorigenicity-2 (sST2) in heart failure patients with reduced ejection fraction (HFrEF).
Methods: In this prospective, observational, multicenter study, patients with heart failure (HF) and left ventricular ejection fraction (LVEF) <50% were included. Clinical evaluation and serum levels of sST2 were estimated at five time points during follow up. Study endpoint was the relationship of baseline and serial sST2 concentration in the blood to the composite endpoints of cardiac death and re-hospitalization for worsening of HF during one year follow up period.
Results: A total of 141 patients were enrolled. The mean age was 60 ± 10.4 years. At baseline evaluation, 49.6% patients were in New York Heart Association (NYHA) class III and 36.2% in class IV. Adverse events were observed in 57 patients (40.4%); 25 (17.7%) were re-hospitalised due to worsening of HF and 32 (22.7%) died due to cardiac causes. The median value of baseline sST2 was 46.36 ng/ml (IQR 31.30–78.38). sST2 concentration at baseline was significantly higher among patients with adverse events in comparison to patients without adverse events (p = <0.001). Receiver operating characteristic curve (ROC) for baseline sST2 concentration identified 49 ng/ml as optimal cut-off value to predict cardiac death and re-hospitalization, with a sensitivity and specificity of 72% and 75% respectively.
Conclusion: In patients with HFrEF, sST2 concentration at baseline as well as on serial testing was significantly correlated with cardiac death and re-hospitalization for worsening of HF.

1. Introduction

Heart failure is a growing health problem worldwide associated with high morbidity and mortality. The overall HF mortality rate remains high with an annual rate of 29.6% and five year rate of 50%.[1] Risk stratification of this multifactorial syndrome is crucial to identify patients who are likely to benefit from the best available and emerging therapies. Biomarkers play an important role in risk stratification of patients with HF.[2,3] Several biomarkers including Brain Natriuretic Peptide (BNP), N-Terminal-proBNP (NT-proBNP), Galectin-3, Soluble endothelin, Growth differentiation factor-15, Copeptin, Suppression of Tumorigenicity-2 (ST2) have been investigated in the diagnosis and prognosis of patients with HF.[4–9]

ST2 is a member of interleukin-1 (IL-1) receptor family which exists in membrane bound (ST2L) and soluble circulating forms (sST2). Binding of interleukin-33 (IL-33) to ST2L has been found to be cardioprotective reducing myocardial fibrosis, hypertrophy and apoptosis in experimental models.[10] sST2 acts as a decoy receptor of IL-33 and eliminates cardioprotective effects of IL-33/ST2L combination in a dose dependent manner. Increased concentration of sST2 in blood has been observed in conditions associated with cardiac fibrosis and remodeling. It has emerged as a strong predictor of cardiovascular outcomes in both acute and chronic HF and its estimation provided incremental value to BNP/NT-proBNP in the diagnosis and prognosis of patients with HF.[11–13] Serial measurement of sST2 has been found to be useful in predicting response to therapy in HF.[8] However, there is a paucity of data on

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Table 1
Demographic and baseline clinical characteristics of the enrolled patients.

	Study population (n = 141)	Patients without adverse outcome (n = 84)	patients with adverse outcome (n = 57)	p-value
Age, years, mean ± SD	60.3 ± 10.4	59.5 ± 10.3	61.6 ± 10.7	0.244
Male, n(%)	108 (76.6)	67 (79.8)	41 (71.9)	0.281
BMI, Kg/m^2, mean ± SD	24.6 ± 3.8	25.1 ± 3.9	24.1 ± 3.8	0.133
Diabetes mellitus	102 (72.3)	53 (63.1)	49 (86)	0.002
Hypertension	84 (59.6)	46 (54.8)	38 (66.7)	0.157
Dyslipidemia	72 (51.1)	34 (40.5)	38 (66.7)	0.0023
Coronary artery disease	78 (55.3)	42 (50)	36 (63.2)	0.123
Cerebrovascular accident	13 (9.2)	7 (8.3)	6 (10.5)	0.658
NYHA class				
II	20 (14.2)	17 (20.2)	3 (5.3)	0.012
III	70 (49.6)	50 (59.5)	20 (35.1)	0.0044
IV	51 (36.2)	17 (20.2)	34 (59.6)	<0.001
IHD	78 (55.3)	42(50)	36(57)	0.123
Non-IHD	63 (44.7)	37 (44)	26 (45.6)	0.35
β-blockers	115 (81.6)	80 (95.2)	35 (61.4)	<0.001
ACEI/ARB	112 (79.4)	76 (90.5)	36 (63.2)	<0.001
Mineralocorticoid receptor Antagonists	81 (57.4)	54 (64.3)	27 (47.4)	0.046
sST2, ng/ml, mean± SD	71.7 ± 83.9	48 ± 36.8	106.6 ± 116.2	<0.001
LVEF%, mean ± SD	31.6 ± 7.1	32.4 ± 7.1	30.3 ± 7	0.087

Adverse events: cardiac-death and rehospitalisation for worsening of HF during one year follow-up.

the prognostic value of sST2 in patients with HFrEF from the Indian subcontinent. This study examined the prognostic value of serum levels of sST2 at five time points during one year in predicting cardiac death and need for re-hospitalization in patients with HFrEF.

2. Methodology

This was a prospective, observational, multicentre study involving three tertiary care hospitals in Kerala, India, enrolling patients who were diagnosed to have HFrEF, between September 2014 and June 2015. The study was approved by the respective institutional ethics committees and informed consent was taken from patients prior to enrolment. Patients with clinical signs and symptoms of HF and left ventricular ejection fraction (LVEF) <50% were included in the study. Exclusion criteria were recent acute coronary syndrome or coronary revascularization in the preceding two months, myocarditis, cardiogenic shock, advanced liver or renal disease, malignancy or any medical condition substantially reducing life expectancy to less than one year.

Clinical examination of all patients was performed during enrolment, at discharge from hospital, one month, six month and one year. Functional status of patients was decided based on NYHA classification. Total cholesterol, HDL, LDL, HbA1c, serum creatinine, potassium, sodium, eGFR, SGOT, SGPT and ALP were estimated at baseline and during follow up visits. Left ventricular functional indices such as LVEF, left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) were determined at baseline echocardiography.

2.1. Biomarker measurement

Blood sample for sST2 estimation was collected at the time of enrolment, at discharge from the hospital, one month, six month and one year visits and the plasma was stored at −70 °C until the time of assay. The sST2 was quantitatively measured using highly sensitive sandwich monoclonal immunoassay (Presage™ ST2 assay, Critical Diagnostics, San Diego, CA)[14] in a single laboratory.

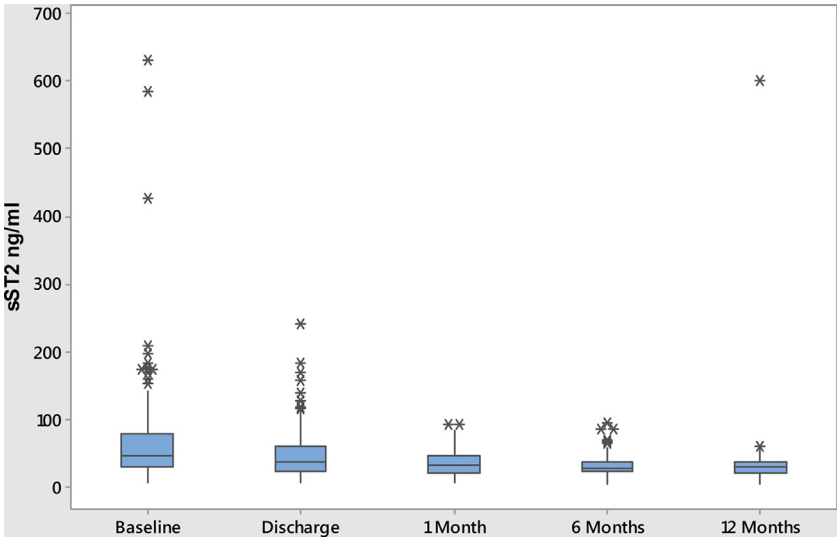

Fig. 1. Distribution of sST2 over time.

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